Application Serial No. 09/567,451
Group Art Unit 1615

EXHIBIT A
CLAIMS WITH MARKINGS TO SHOW CHANGES

1. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.

3. (Amended) A method of treatment of a patient's hypertension and/or angina comprising administration of a preparation of claim 1 [or 2] in the night to a patient for effect the next morning and which formulation exhibits a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given with food and without food according to the same FDA guidelines or criteria.

4. (Amended) The controlled-release Galenical preparation of claim 1 [or 2] wherein the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours; and

(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours.

5. (Amended) The controlled-release Galenical preparation of claim [1 or] 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours.

6. (Amended) The preparation of claim [1, 2,] 4 [or 5] wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

8. (Amended) The preparation of claim [1, 2, 4, 5,] 6 [or 7] wherein the preparation is a diffusion controlled preparation.

9. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7 or 8] wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

10. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8 or] 9 in capsule form.

11. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8 or] 9 in tablet form.

12. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8,] 9[, 10 or 11] wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

14. (Amended) The preparation of claim 13 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each <u>microgranule</u> [bead], ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

15. (Amended) The preparation of claim [12, 13 or] 14 wherein the membrane comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.

16. (Amended) The preparation of claim 12 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.

17. (Amended) The preparation of claim [12, 13, 14, 15 or] 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30D] and hydroxypropylmethylcellulose.

18. (Amended) The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule [bead], and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

19. (Amended) The preparation of claim 13 [or 14] wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane [Eudragit RS, Eudragit RL] and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

20. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8,] 9[, 10 or 11] wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

21. (Amended) The preparation of claim 20 wherein the dissolution agent is an organic acid comprising [such as] adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid[,] or tartaric acid [and the like] which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the [higher pH] regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

41. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 120 mg of Diltiazem.

42. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 180 mg of Diltiazem.

43. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 17 or 17] wherein the preparation contains 240 mg of Diltiazem.

44. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 300 mg of Diltiazem.

45. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 360 mg of Diltiazem.

46. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 420 mg of Diltiazem.

48. (Amended) The preparation of claim [12, 13, 14, 15, 16,] 17[, 18 or 19] wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose, <u>including</u> [commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.) such as] sucrose stearate [marketed under the trade name of Crodesta];
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene [(Brijs, Renex and Eumulgines, Henkel, RFA)];
sorbitan fatty acid esters [(Span, Atlas, U.S.A.)];
polyglycides-glycerides and polyglycides-alcohols esters [(Gelucires, Gattefosse, France)]
Metal salts [such as NaCl or sodium lauryl sulphate].

49. (Amended) The preparation of claim 12 wherein the wetting agent is in association with the diltiazem in the microgranule [bead] and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [such as Eudragit NE30D] enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

52. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent [The preparation of claim 12, 13, 14, 15, 16, 17, 18, 19, 48 or 49] in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)8 - 9.5	
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0

(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

54. (Amended) The preparation of claim 12[, 13, 14, 15, 16, 17, 18, 19, 48 or 49] in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

56. (Amended) The preparation of claim 12[, 13, 14, 15, 16, 17, 18, 19, 48 or 49] in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

58. (Amended) The preparation of claim 12[, 13, 14, 15, 16, 17, 18, 19, 48 or 49] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

59. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

60. (Amended) The controlled-release Galenical preparation of claim [1 or] 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

63. (Amended) The preparation of claim 60[, 61 or 62] wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

64. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time

wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

[The preparation of claim 60, 61 or 62] wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)8 - 9.5	
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5

(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

65. (Amended) The preparation of claim 60[, 61, 62, 63 or 64] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

66. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 60[, 61, 62, 63, 64 or 65] to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

67. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.

68. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours.

69. (Amended) The preparation of claim [67 or] 68 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

70. (Amended) The preparation of claim [67,] 68 [or 69] wherein the Diltiazem is in the form of Diltiazem HCl.

71. (Amended) The preparation of claim [67,] 68[, 69 or 70] wherein the preparation is a diffusion controlled preparation.

72. (Amended) The preparation of claim [67,] 68[, 69, 70 or 71] wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

73. (Amended) The preparation of claim [67,] 68[, 69, 70, 71 or 72] in capsule form.

74. (Amended) The preparation of claim [67,] 68[, 69, 70, 71 or 72] in tablet form.

75. (Amended) The preparation of claim 67[, 68, 69, 70, 71, 72, 73 or 74] wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

77. (Amended) The preparation of claim 76 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each <u>microgranule</u> [bead], ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

78. (Amended) The preparation of claim [75, 76 or] 77 wherein the membrane comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.

79. (Amended) The preparation of claim 75 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.

80. (Amended) The preparation of claim [75, 76,] 77[, 78 or 79] wherein the membrane comprises Eudragit NE30D and hydroxypropylmethylcellulose.

81. (Amended) The preparation of claim 80 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the <u>microgranule</u> [bead], and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

82. (Amended) The preparation of claim [76 or] 77 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises <u>an acrylic polymer</u> [Eudragit RS, Eudragit RL] and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

83. (Amended) The preparation of claim [67,] 68[, 69, 70, 71, 72, 73 or 74] wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof

associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

84. (Amended) The preparation of claim 83 wherein the dissolution agent is an organic acid comprising [such as] adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid[,] or tartaric acid [and the like] which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the [higher pH] regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

103. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 120 mg of Diltiazem.

104. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 180 mg of Diltiazem.

105. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 240 mg of Diltiazem.

106. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 300 mg of Diltiazem.

107. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 360 mg of Diltiazem.

108. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 420 mg of Diltiazem.

110. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which

the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:
(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, [The preparation of claim 75, 76, 77, 78, 79, 80, 81 or 82] wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose, commercialized under the name of sucroesters [(Gattefosse, France)] or under the name of crodesters [(Croda, U.K.)] such as sucrose stearate marketed under the trade name of Crodesta;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene [(Brijs, Renex and Eumulgines, Henkel, RFA)];
sorbitan fatty acid esters [(Span, Atlas, U.S.A.)];

polyglycides-glycerides and polyglycides-alcohols esters [(Gelucires, Gattefosse, France)]
Metal salts [such as NaCl or sodium lauryl sulphate].

111. (Amended) The preparation of claim 75 wherein the wetting agent is in association with the diltiazem in the microgranule [bead] and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [such as Eudragit NE30D] enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

114. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:
(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, [The preparation of claim 75, 76, 77, 78, 79, 80, 81, 82, 110 or 111] in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

116. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, [The preparation of claim 75, 76, 77, 78, 79, 80, 81, 82, 110 or 111] in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

118. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core

containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, [The preparation of claim 75, 76, 77, 78, 79, 80, 81, 82, 110 or 111] in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

120. (Amended) The preparation of claim [75, 76,] 77[, 78, 79, 80, 81, 82, 110 or 111] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

122. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof,

suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

125. (Amended) The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

127. (Amended) The preparation of claim 122[,] or 124[, 125 or 126] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

128. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 122, 123[,] or 124[, 125, 126 or 127] to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Application Serial No. 09/567,451
Group Art Unit 1615

EXHIBIT B
CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT

1. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.

2. The controlled release Galenical preparation of claim 1 wherein the higher bioavailability achieved after night administration of the preparation than morning administration without food exceeds 25% C_{max}.

3. (Amended) A method of treatment of a patient's hypertension and/or angina comprising administration of a preparation of claim 1 in the night to a patient for effect the next morning and which formulation exhibits a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given with food and without food according to the same FDA guidelines or criteria.

4. (Amended) The controlled-release Galenical preparation of claim 1 wherein the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.

2 cont.

5. (Amended) The controlled-release Galenical preparation of claim 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours.

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6. (Amended) The preparation of claim 4 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

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7. The preparation of claim 1, 2, 4, 5 or 6 wherein the Diltiazem is in the form of Diltiazem HCl.

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8. (Amended) The preparation of claim 6 wherein the preparation is a diffusion controlled preparation.

9. (Amended) The preparation of claim 5 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

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10. (Amended) The preparation of claim 9 in capsule form.

11. (Amended) The preparation of claim 9 in tablet form.

12. (Amended) The preparation of claim 9 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

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13. The preparation of claim 12 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

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14. (Amended) The preparation of claim 13 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

15. (Amended) The preparation of claim 14 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

16. (Amended) The preparation of claim 12 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

17. (Amended) The preparation of claim 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

18. (Amended) The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

19. (Amended) The preparation of claim 13 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

20. (Amended) The preparation of claim 9 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

21. (Amended) The preparation of claim 20 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

22. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 1 or 2 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

23. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 4 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

24. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

25. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 6 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

26. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

27. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

28. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

29. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 10 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

30. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

31. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

32. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

33. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

34. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

35. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 16 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

36. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

37. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

38. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 19 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

39. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 20 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

40. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 21 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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41. (Amended) The preparation of claim 5 wherein the preparation contains 120 mg of Diltiazem.

42. (Amended) The preparation of claim 5 wherein the preparation contains 180 mg of Diltiazem.

43. (Amended) The preparation of claim 5 wherein the preparation contains 240 mg of Diltiazem.

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44. (Amended) The preparation of claim 5 wherein the preparation contains 300 mg of Diltiazem.

45. (Amended) The preparation of claim 5 wherein the preparation contains 360 mg of Diltiazem.

46. (Amended) The preparation of claim 5 wherein the preparation contains 420 mg of Diltiazem.

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47. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 41, 42, 43, 44, 45 or 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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48. (Amended) The preparation of claim 17 wherein the wetting agent is selected from:

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sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose, including sucrose stearate;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid ester;
polyglycides-glycerides and polyglycides-alcohols esters
Metal salts.

49. (Amended) The preparation of claim 12 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

50. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

51. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 49 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

52. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core

comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

53. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

54. (Amended) The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

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(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

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55. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 54 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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56. (Amended) The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

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(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

57. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

58. (Amended) The preparation of claim 12 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

59. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

60. (Amended) The controlled-release Galenical preparation of claim 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

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together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

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61. The preparation of claim 60 wherein the microgranules are in capsule form.

62. The preparation of claim 60 wherein the microgranules are in tablet form.

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63. (Amended) The preparation of claim 60 wherein the core and membrane comprise:

(i) in the core,

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(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

64. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11

~~Purified water USP 0 (used for mixing).~~

65. (Amended) The preparation of claim 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

66. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 60 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

67. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.

68. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours.

69. (Amended) The preparation of claim 68 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

70. (Amended) The preparation of claim 68 wherein the Diltiazem is in the form of Diltiazem HCl.

71. (Amended) The preparation of claim 68 wherein the preparation is a diffusion controlled preparation.

72. (Amended) The preparation of claim 68 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

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73. (Amended) The preparation of claim 68 in capsule form.

74. (Amended) The preparation of claim 68 in tablet form.

75. (Amended) The preparation of claim 67 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

76. The preparation of claim 75 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

77.. (Amended) The preparation of claim 76 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

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78. (Amended) The preparation of claim 77 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

79. (Amended) The preparation of claim 75 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting

agent and the membrane comprises a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

80. (Amended) The preparation of claim 77 wherein the membrane comprises Eudragit NE30D and hydroxypropylmethylcellulose.

81. (Amended) The preparation of claim 80 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

82. (Amended) The preparation of claim 77 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic polymer and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

83. (Amended) The preparation of claim 68 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

84. (Amended) The preparation of claim 83 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

85. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 67 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

86. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 68 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

87. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 69 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

88. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 70 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

89. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 71 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

90. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 72 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

91. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 73 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

92. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 74 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

93. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 75 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

94. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 76 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

95. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 77 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

96. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 78 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

97. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 79 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

98. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 80 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

99. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 81 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

100. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 82 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

101. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 83 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

102. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 84 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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103. (Amended) The preparation of claim 68 wherein the preparation contains 120 mg of Diltiazem.

104. (Amended) The preparation of claim 68 wherein the preparation contains 180 mg of Diltiazem.

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105. (Amended) The preparation of claim 68 wherein the preparation contains 240 mg of Diltiazem.

106. (Amended) The preparation of claim 68 wherein the preparation contains 300 mg of Diltiazem.

107. (Amended) The preparation of claim 68 wherein the preparation contains 360 mg of Diltiazem.

108. (Amended) The preparation of claim 68 wherein the preparation contains 420 mg of Diltiazem.

109. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 103, 104, 105, 106, 107 or 108 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

110. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the

central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose, commercialized under the name of sucroesters or under the name of crodesters such as sucrose stearate marketed under the trade name of Crodesta;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid esters;
polyglycides-glycerides and polyglycides-alcohols esters
Metal salts.

111. (Amended) The preparation of claim 75 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

112. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 110 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

113. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 111 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

114. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 15% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate	7 - 8

(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

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115. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 112 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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116. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

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117. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 116 to the patient in the

evening for effective treatment of the patient's hypertension and/or angina the next morning.

118. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

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119. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 118 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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120. (Amended) The preparation of claim 77 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

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121. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 120 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

122. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

123. The preparation of claim 122 wherein the microgranules are in capsule form.

124. The preparation of claim 122 wherein the microgranules are in tablet form.

125. (Amended) The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

126. The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30	1 - 2

(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	Eudragit NE30 D (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

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127. (Amended) The preparation of claim 122 or 124 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

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128. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 122, 123 or 124 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

APPROVED BY DRAFTSMAN	O.G. FIG. CLASS	SUBCLASS

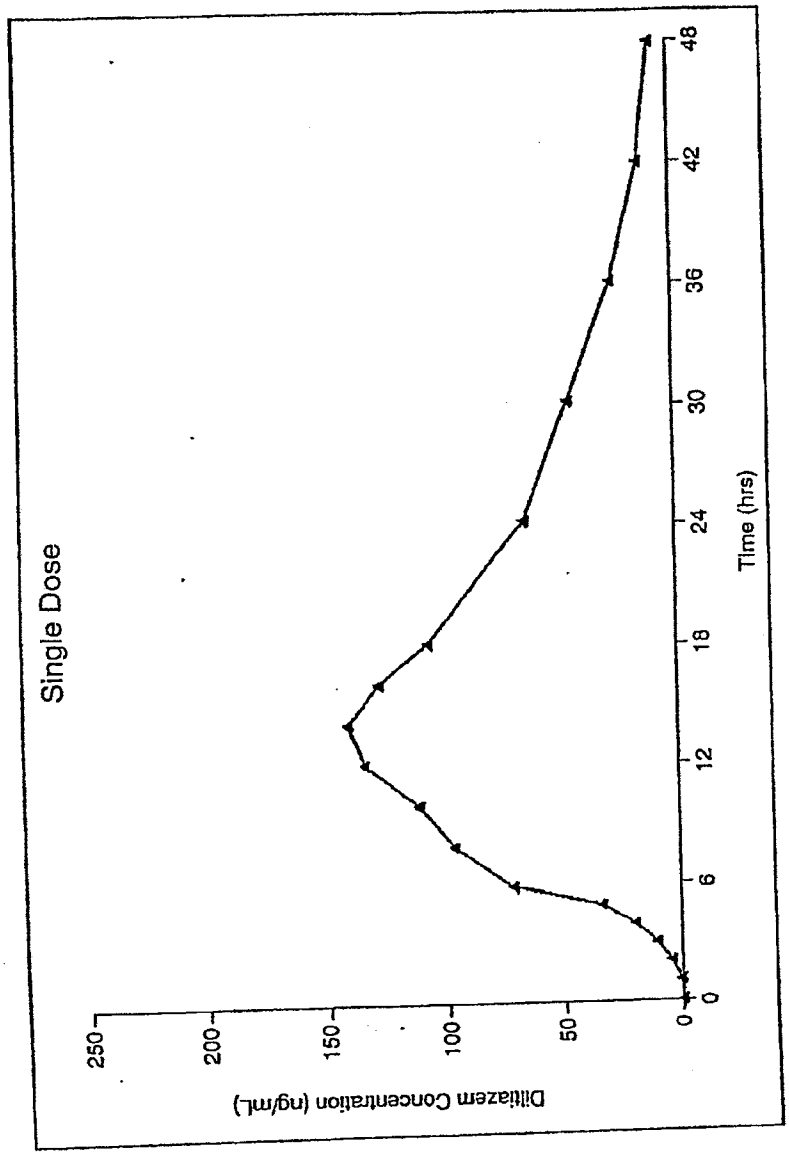

Fig. 1

APPROVED BY DRAFTSMAN	O.G. FIG. CLASS	SUBCLASS

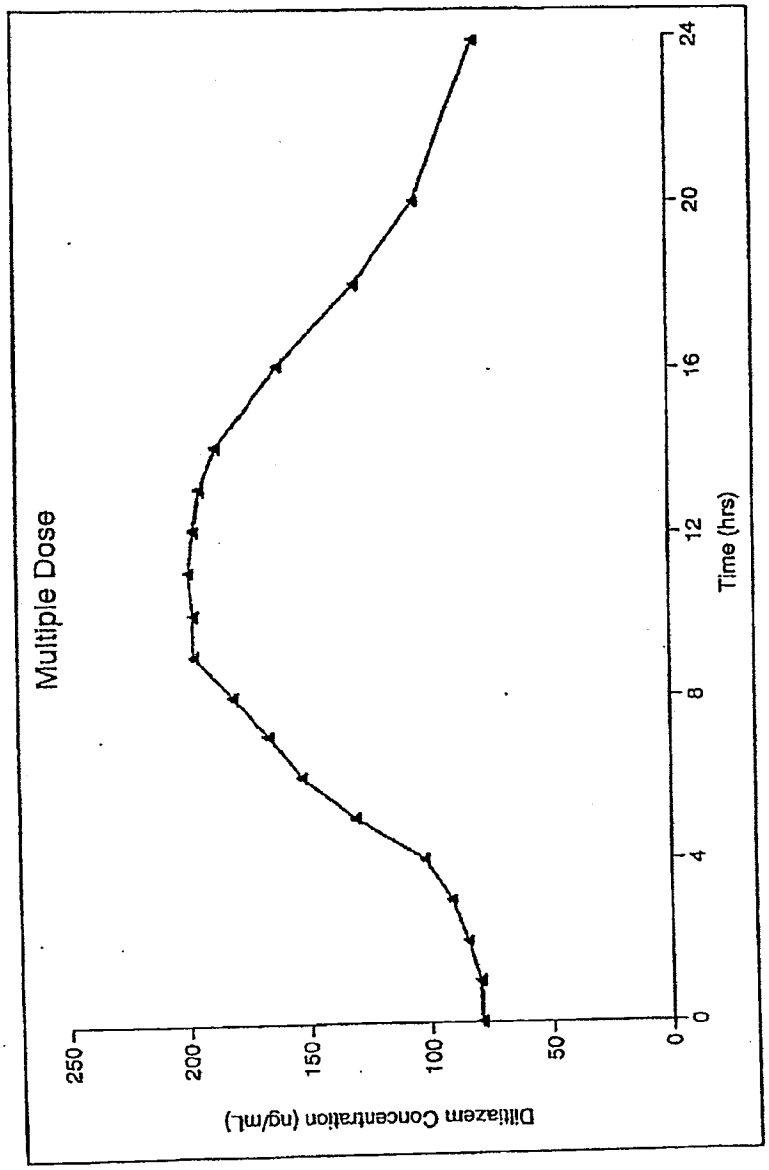

Fig. 2

APPROVED BY DRAFTSMAN	O.G. FIG. CLASS	SUBCLASS

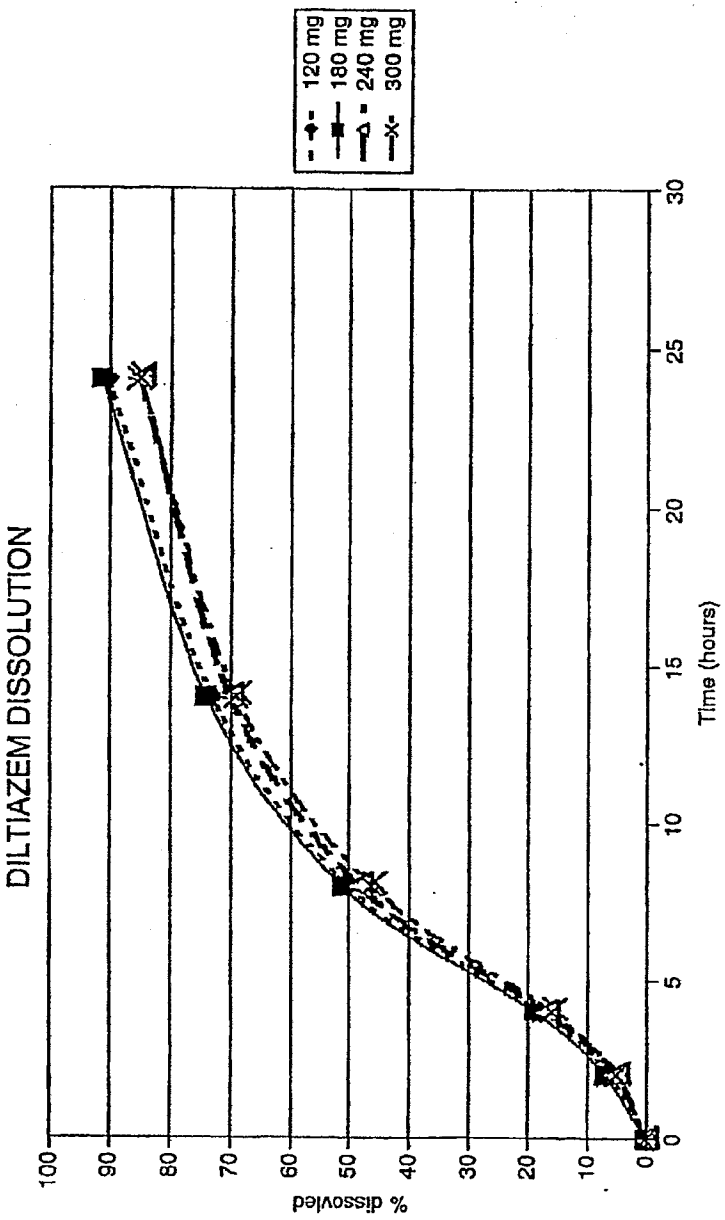

Fig. 3

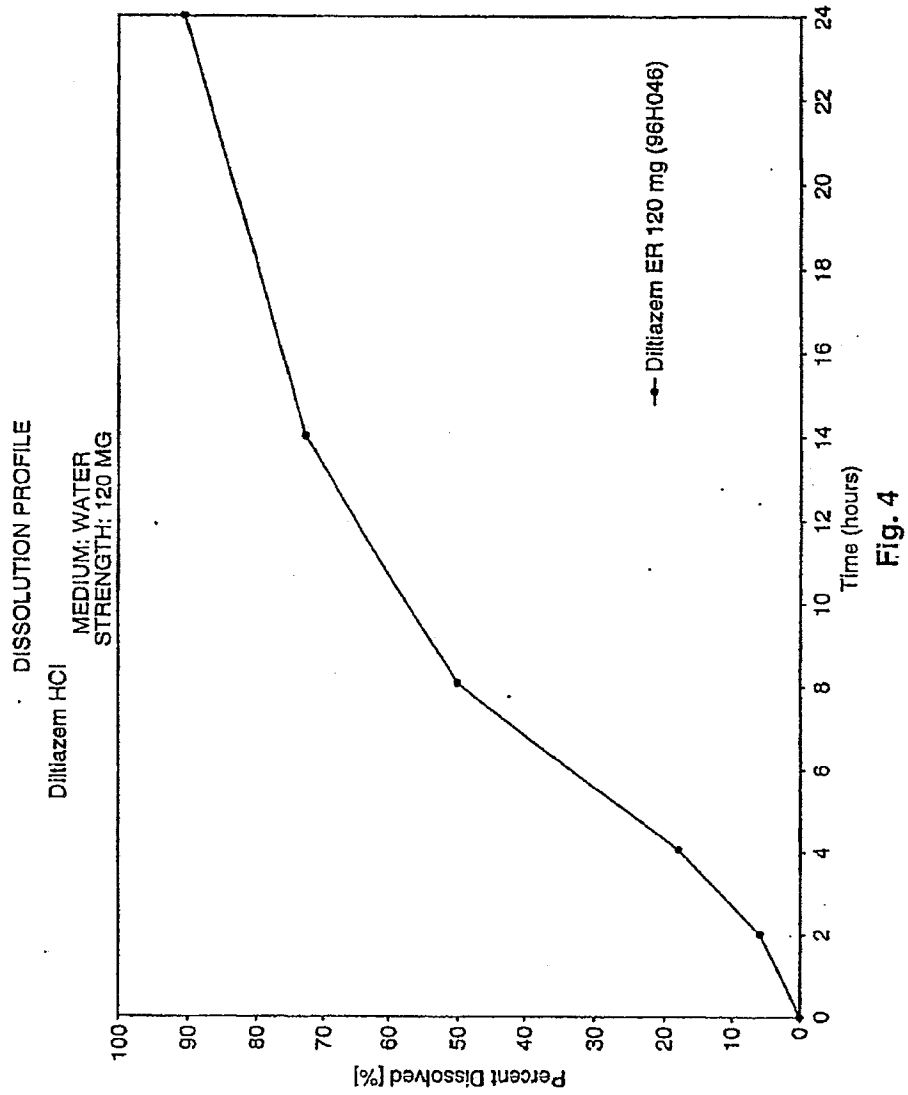

Fig. 4

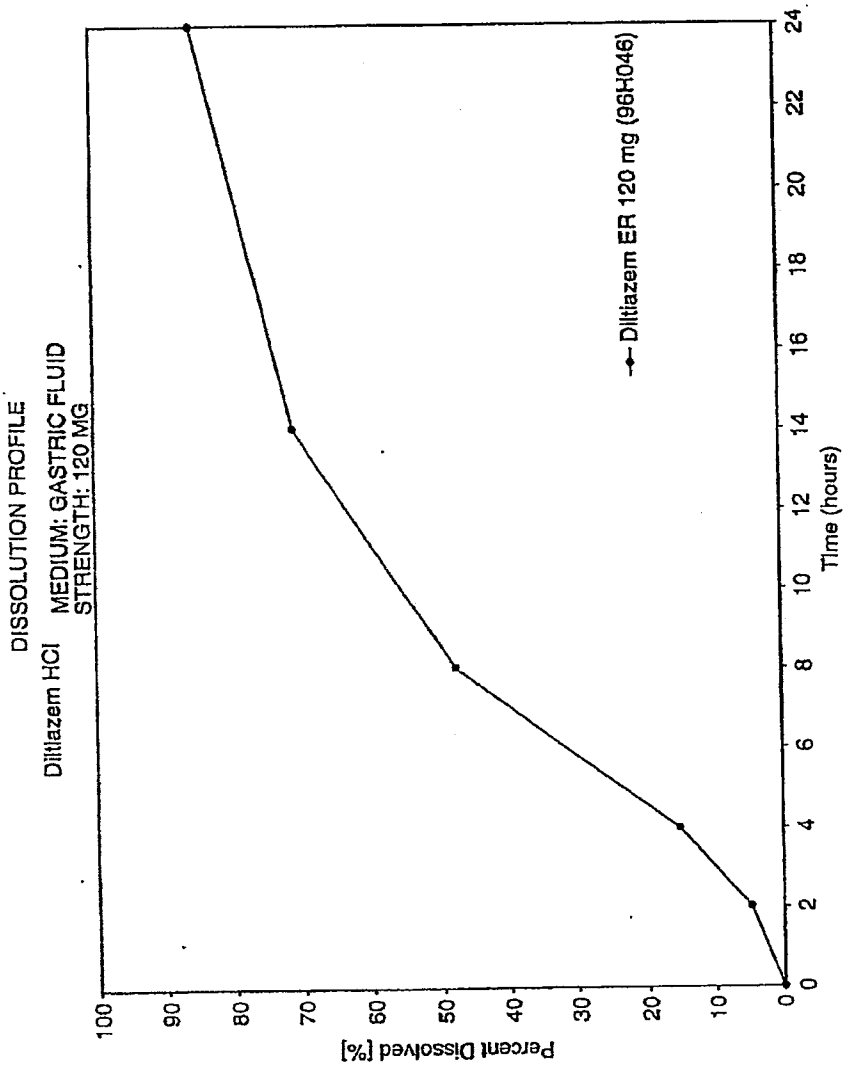

Fig. 5

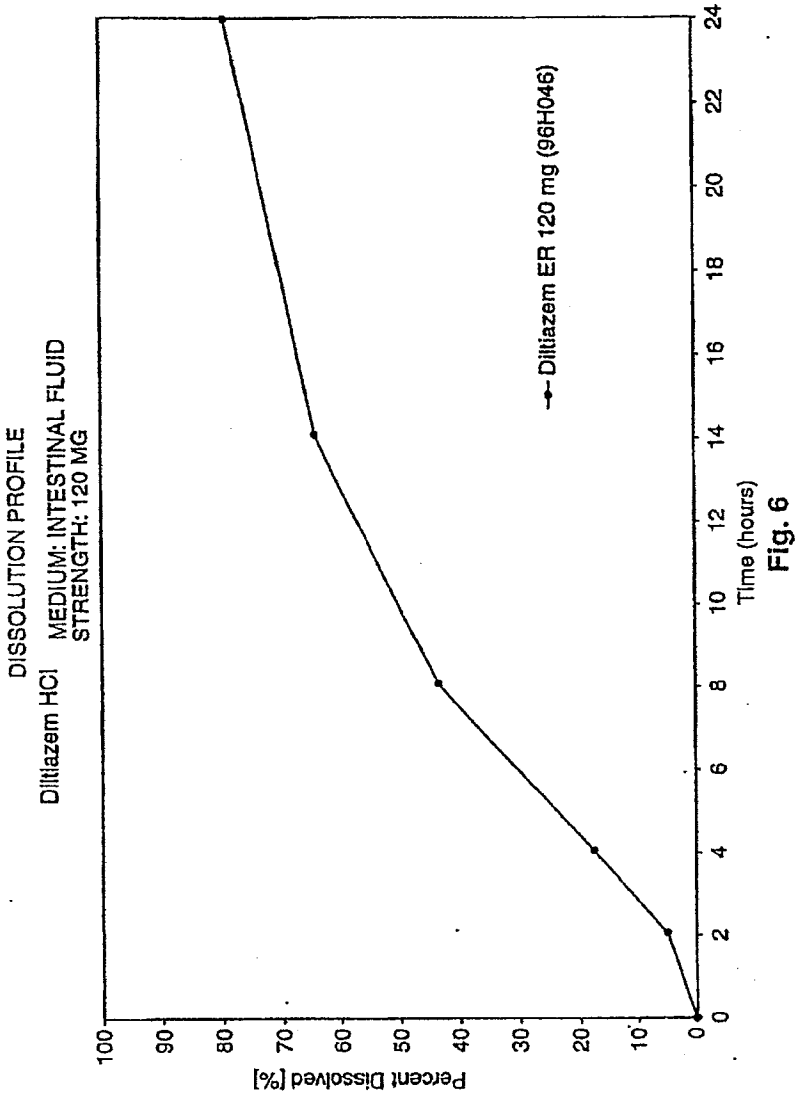

Fig. 6

APPROVED BY DRAFTSMAN	O.G. FIG. CLASS	SUBCLASS

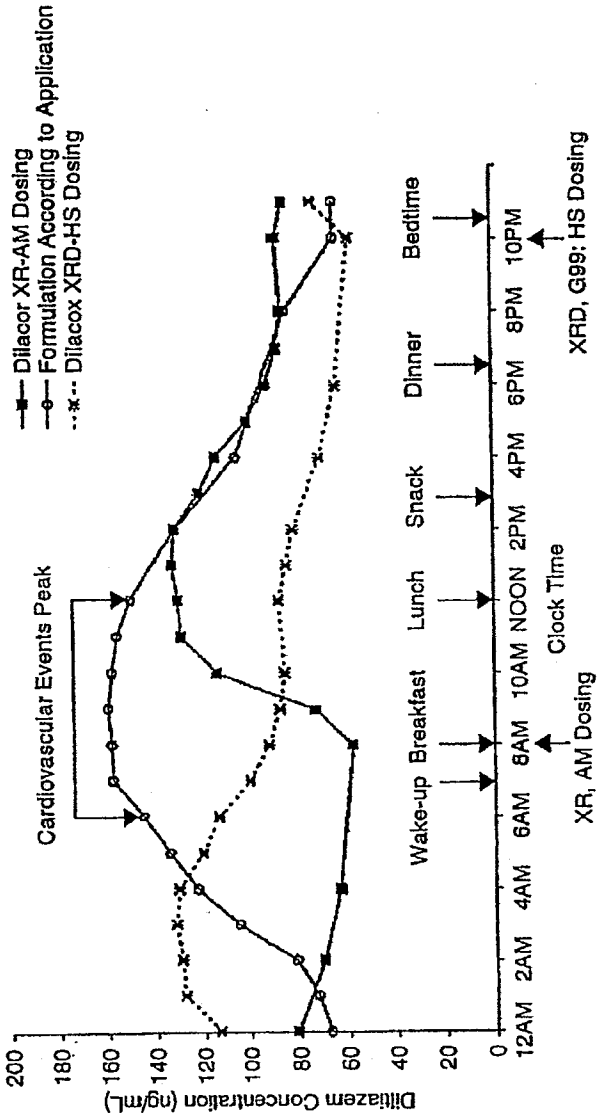

Fig. 7

APPROVED BY DRAFTSMAN	O.G. FIG. CLASS	SUBCLASS

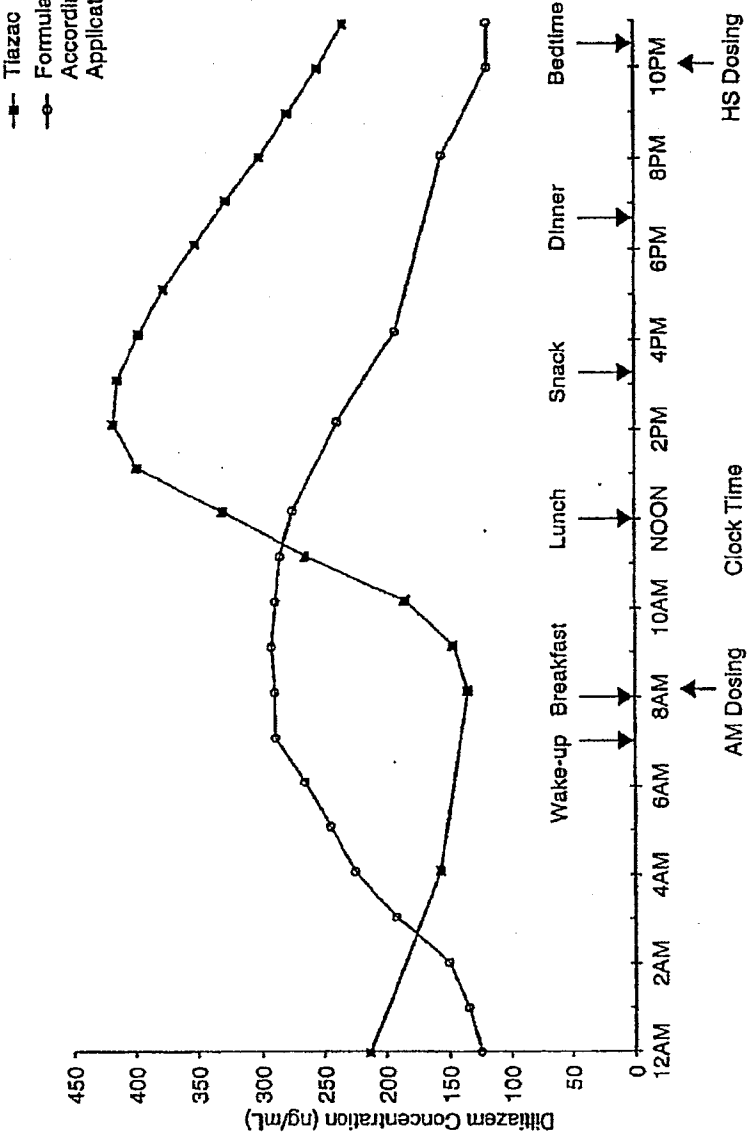

Fig. 8

APPROVED BY DRAFTSMAN	O.G. FIG. CLASS	SUBCLASS

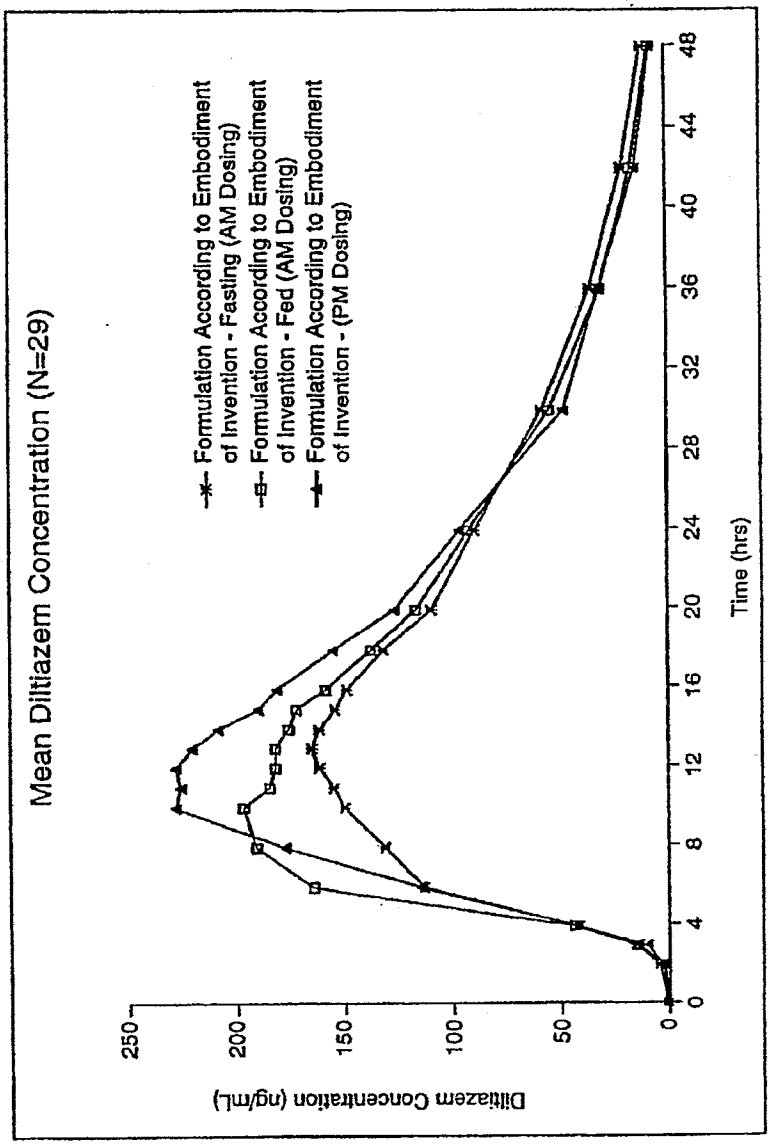

Fig. 9

Diltiazem AUCt PK Summary

Formulation According to Embodiment of Invention

Subject	Morning Fasting AUCt	Morning Fasting Log AUCt	Morning Fed AUCt	Morning Fed Log AUCt	Night Dosing AUCt	Night Dosing Log AUCt	Morning Fed/Fast Ratio	Night/Morning Ratio
2	1730.75	7.46	2647.15	7.88	1987.11	7.59	1.53	1.15
3	2712.98	7.91	2336.67	7.76	3248.94	8.09	0.86	1.20
4	2588.34	7.90	1907.61	7.55	2692.21	7.97	0.71	1.08
5	4192.37	8.34	4108.65	8.32	4702.33	8.46	0.98	1.12
6	3074.51	8.03	2887.98	7.97	3900.06	8.27	0.94	1.27
7	1629.81	7.40	1847.56	7.52	2723.36	7.91	1.13	1.67
8	941.10	6.85	1970.97	7.59	1835.11	7.51	2.09	1.95
9	3144.13	8.05	3462.59	8.15	2923.86	7.98	1.10	0.93
10	2074.94	7.64	2997.45	8.01	4028.83	8.30	1.44	1.94
11	3853.96	8.20	2771.53	7.93	3464.72	8.15	0.76	0.95
12	2684.22	7.90	3790.43	8.24	3141.47	8.05	1.41	1.17
13	3352.69	8.12	3751.95	8.23	3708.83	8.22	1.12	1.11
14	2988.61	8.00	3665.60	8.21	3141.05	8.05	1.23	1.05
15	6796.97	8.82	8204.22	9.01	7578.33	8.93	1.21	1.11
16	2873.70	7.96	4644.79	8.44	4182.09	8.34	1.62	1.46
17	4468.33	8.40	4222.55	8.35	3762.50	8.23	0.94	0.84
18	5654.29	8.64	5635.72	8.64	7159.38	8.88	1.00	1.27
19	4944.07	8.51	5107.44	8.54	4812.20	8.48	1.03	0.97
20	2986.73	8.00	2988.34	8.00	2791.23	7.93	1.00	0.93
21	2908.88	7.98	3314.12	8.11	4389.98	8.39	1.14	1.51
22	4270.43	8.36	3790.06	8.24	3631.01	8.20	0.89	0.85
23	6150.18	8.72	6092.56	8.71	7478.22	8.92	0.99	1.22
25	2926.46	7.98	5633.64	8.64	4839.10	8.48	1.93	1.65
26	3928.61	8.28	4614.43	8.44	4359.77	8.38	1.17	1.11
27	3637.94	8.20	4587.48	8.43	4063.15	8.31	1.26	1.12
28	4177.76	8.34	4945.31	8.51	6689.14	8.81	1.18	1.60
29	3609.69	8.19	2720.67	7.91	2163.20	7.68	0.75	0.60
30	4483.17	8.41	5222.54	8.56	5587.50	8.63	1.16	1.25
32	4058.04	8.31	3531.47	8.17	3052.87	8.03	0.87	0.76
Mean	3542.88	8.10	3910.40	8.21	4078.57	8.25	1.15	1.20
SD	1304.23	0.41	1431.24	0.36	1554.69	0.37	0.33	0.33
CV	36.81	5.08	36.60	4.43	38.12	4.46	28.23	27.33
Median	3352.69	8.12	3751.95	8.23	3762.50	8.23	1.12	1.12
Geo Mean	3292.83	8.09	3671.24	8.20	3818.30	8.24	1.11	1.16

Fed/Fasting Ratio (Morning Dosing)			Night/Morning Ratio	
Ratio of Means	1.10	#	Ratio of Means	1.15
Ratio of Geo Means	1.11	#	Ratio of Geo Means	1.16
Avg of Individual Ratio	1.15	#	Avg of Individual Ratios	1.20

Fig. 9A

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

Diltiazem Cmax PK Summary

Formulation According to Embodiment of Invention

Subject	Morning Fasting Tmax	Morning Fasting Cmax	Morning Fasting Log Cmax	Morning Fed Tmax	Morning Fed Cmax	Morning Fed Log Cmax	Night Dosing Tmax	Night Dosing Cmax	Night Dosing Log Cmax	Morning Fed/Fast Ratio	Night/Morning Ratio
2	10.0	88.53	4.69	10.0	167.71	5.23	13.0	143.84	4.97	1.90	1.46
3	13.0	136.16	4.91	11.0	123.04	4.81	10.0	246.57	5.51	0.90	1.81
4	15.0	133.23	4.89	10.0	118.66	4.76	10.0	191.44	5.25	0.89	1.44
5	8.0	222.52	5.41	8.0	195.88	5.28	12.0	254.96	5.54	0.88	1.15
6	12.0	150.95	5.02	8.0	164.11	5.10	16.0	170.67	5.19	1.09	1.19
7	10.0	90.68	4.51	14.0	121.64	4.80	12.0	170.67	5.19	1.34	1.98
8	8.0	85.56	4.18	11.0	119.30	4.78	11.0	133.33	4.89	1.82	2.03
9	13.0	155.46	5.05	8.0	292.70	5.68	12.0	175.62	5.17	1.88	1.13
10	8.0	95.45	4.56	8.0	188.81	5.12	13.0	196.94	5.28	1.75	2.08
11	14.0	212.41	5.36	11.0	164.64	5.04	14.0	163.56	5.21	0.73	0.66
12	10.0	117.75	4.77	10.0	201.43	5.31	11.0	174.68	5.16	1.71	1.48
13	14.0	148.90	5.01	13.0	185.51	5.24	10.0	208.76	5.34	1.26	1.39
14	13.0	139.54	4.94	8.0	205.35	5.32	13.0	187.32	5.23	1.47	1.34
15	16.0	266.46	5.59	15.0	330.53	5.80	13.0	459.34	6.11	1.24	1.69
16	13.0	134.55	4.90	8.0	281.74	5.64	10.0	238.10	5.48	2.09	1.75
17	12.0	224.65	5.41	10.0	244.82	5.50	14.0	203.51	5.32	1.09	0.91
18	14.0	261.88	5.54	8.0	308.25	5.73	13.0	478.11	6.17	1.09	1.70
19	15.0	227.89	5.43	11.0	262.82	5.57	13.0	231.49	5.44	1.15	1.02
20	14.0	137.54	4.92	10.0	176.76	5.17	10.0	173.53	5.16	1.28	1.26
21	13.0	184.75	5.10	13.0	197.53	5.28	13.0	391.72	5.71	1.20	1.83
22	16.0	182.52	5.21	11.0	207.19	5.33	10.0	247.06	5.51	1.14	1.35
23	16.0	259.97	5.60	10.0	340.21	5.83	10.0	500.62	6.22	1.26	1.86
25	10.0	166.06	5.11	8.0	322.55	5.78	10.0	263.27	5.57	1.94	1.59
26	13.0	208.16	5.34	10.0	237.60	5.47	10.0	235.12	5.46	1.14	1.13
27	10.0	182.47	5.09	8.0	255.85	5.54	10.0	170.18	5.14	1.57	1.05
28	13.0	210.58	5.39	11.0	236.10	5.46	11.0	384.02	5.95	1.08	1.76
29	13.0	215.15	5.37	13.0	160.73	5.08	12.0	128.94	4.87	0.75	0.60
30	14.0	242.66	5.49	12.0	244.58	5.50	10.0	338.54	5.82	1.01	1.39
32	12.0	303.43	5.72	15.0	204.09	5.32	11.0	231.33	5.44	0.67	0.76
Mean	12.6	178.45	5.13	10.3	215.53	5.33	11.8	242.46	5.42	1.29	1.41
SD	2.5	61.85	0.37	2.5	64.85	0.31	1.6	88.98	0.36	0.40	0.39
CV	19.8	34.66	7.23	24.3	30.09	5.83	14.1	40.82	6.58	30.69	27.83
Median	13.0	184.75	5.10	10.0	204.09	5.32	11.0	208.76	5.34	1.20	1.39
Geo Mean	12.3	167.47	5.11	9.9	206.00	5.32	11.4	228.63	5.41	1.23	1.35

Fed/Fasting Ratio (Morning Dosing)

Ratio of Means	1.21
Ratio of Geo Means	1.23
Avg of Individual Ratios	1.29

Night/Morning Ratio

Ratio of Means	1.38
Ratio of Geo Means	1.35
Avg of Individual Ratios	1.41

Fig. 9B

APPROVED BY DRAFTSMAN	O.G. FIG. CLASS	SUBCLASS

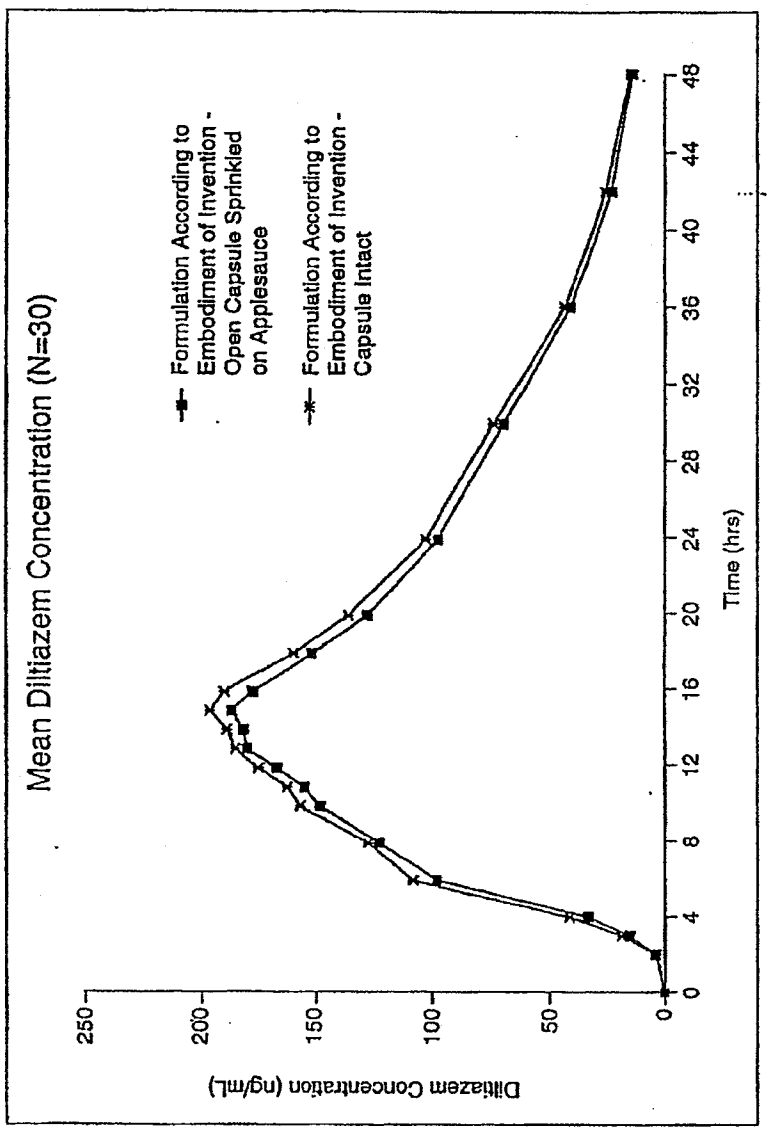

Fig. 10

APPROVED BY DRAFTSMAN	O.G. FIG. CLASS	SUBCLASS

PK Summary (N=30)

Diltiazem PK

Open Capsule Sprinkled on Applesauce / Capsule Intact

AUCt

Ratio of Means %	94.16
Ratio of Geo Means %	93.98
Avg of Individual Ratios %	96.03
90% C.I.	88%-99%
Intra-CV	13.47%

Cmax

Ratio of Means %	93.35
Ratio of Geo Means %	93.00
Avg of Individual Ratios %	95.73
90% C.I.	86%-99%
Intra-CV	16.07%

Tmax

	Mean
Open Capsule Sprinkled on Applesauce	13.7 hours
Capsules Intact	13.5 hours

Fig. 10A

BY	CLASS	SUBCLASS
DRAFTSMAN		

Diltiazem AUCt Results

Formulation According to Embodiment of Invention

	Open Capsules Sprinkled on Applesauce (A)		Capsule Intact (B)		(A:B)
Subject	AUCt	Log Cmax	AUCt	Log Cmax	Ratio
1	3937.18	8.28	3251.62	8.09	1.21
2	3782.89	8.24	5502.18	8.61	0.69
3	1616.35	7.39	2358.22	7.77	0.69
4	8209.44	9.01	7954.29	8.98	1.03
5	2171.26	7.68	2452.78	7.80	0.89
6	5710.90	8.65	7082.30	8.87	0.81
7	1983.56	7.59	2624.03	7.87	0.76
8	3862.46	8.26	3114.53	8.04	1.24
9	6069.65	8.71	4585.60	8.43	1.32
10	3907.33	8.27	6393.14	8.76	0.61
11	3842.58	8.25	4292.30	8.36	0.90
12	4873.82	8.49	6493.87	8.78	0.75
13	2707.85	7.90	3922.90	8.27	0.69
14	2553.27	7.85	2159.88	7.68	1.18
15	2042.47	7.62	2902.70	7.97	0.70
16	4650.14	8.44	4769.32	8.47	0.98
17	3705.72	8.22	3464.89	8.15	1.07
19	7881.69	8.97	6851.45	8.83	1.15
21	6151.00	8.72	6282.65	8.75	0.98
22	2138.64	7.67	1933.52	7.57	1.11
23	3983.50	8.29	5177.74	8.55	0.77
24	3939.51	8.28	3517.56	8.17	1.12
25	2318.36	7.75	2016.26	7.61	1.15
27	2061.09	7.63	1928.02	7.56	1.07
28	2871.31	7.96	3312.87	8.11	0.87
29	4305.14	8.37	3559.57	8.18	1.21
30	3190.17	8.07	3565.88	8.18	0.89
31	3422.16	8.14	3012.17	8.01	1.14
33	4906.47	8.50	5206.52	8.56	0.94
34	2969.19	8.00	3255.28	8.09	0.91
Mean	3859.17	8.17	4098.47	8.24	0.96
SD	1664.90	0.42	1708.24	0.41	0.20
CV	43.14	5.10	41.68	5.03	20.69
Median	3817.74	8.25	3538.57	8.17	0.96
Geo Mean	3546.16	8.16	3773.43	8.23	0.94

Test/Ref Ratio	
Ratio of Means %	94.16
Ratio of Geo Means %	93.98
Avg of Individual Ratios	0.96
90% C.I.	88%-99%
Intra-CV	13.47%

Fig. 10B

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

Diltiazem Cmax Results

Formulation According to Embodiment of Invention

	Open Capsule Sprinkled on Applesauce (A)			Capsule Intact (B)			(A:B)
Subject	Tmax	Cmax	Log Cmax	Tmax	Cmax	Log Cmax	Ratio
1	13.0	184.35	5.22	13.0	228.99	5.43	0.81
2	14.0	192.44	5.26	12.0	286.72	5.66	0.67
3	13.0	103.87	4.64	12.0	127.07	4.84	0.82
4	10.0	372.93	5.92	8.0	298.05	5.70	1.25
5	14.0	107.71	4.68	16.0	147.84	5.00	0.73
6	13.0	244.87	5.50	15.0	315.48	5.75	0.78
7	14.0	115.23	4.75	16.0	135.27	4.91	0.85
8	13.0	257.26	5.55	15.0	179.11	5.19	1.44
9	8.0	232.12	5.45	10.0	194.37	5.27	1.19
10	16.0	172.20	5.15	15.0	281.81	5.64	0.61
11	13.0	177.41	5.18	8.0	181.17	5.20	0.98
12	13.0	225.55	5.42	10.0	327.23	5.79	0.69
13	15.0	135.86	4.91	15.0	213.37	5.36	0.64
14	15.0	154.65	5.04	14.0	135.94	4.91	1.14
15	12.0	114.81	4.74	15.0	181.80	5.20	0.63
16	15.0	294.21	5.68	13.0	296.58	5.69	0.99
17	15.0	187.32	5.23	15.0	183.62	5.21	1.02
19	16.0	385.36	5.95	15.0	376.57	5.93	1.02
21	15.0	318.06	5.76	10.0	276.15	5.62	1.15
22	14.0	114.40	4.74	14.0	97.24	4.58	1.18
23	12.0	260.20	5.56	12.0	346.74	5.85	0.75
24	14.0	211.61	5.35	16.0	202.88	5.31	1.04
25	14.0	155.98	5.05	15.0	125.66	4.83	1.24
27	16.0	79.66	4.38	16.0	67.35	4.21	1.18
28	16.0	124.76	4.83	16.0	165.01	5.11	0.76
29	15.0	225.58	5.42	10.0	164.02	5.10	1.38
30	14.0	166.54	5.12	15.0	165.41	5.11	1.01
31	15.0	134.14	4.90	14.0	135.19	4.91	0.99
33	13.0	282.10	5.64	16.0	275.33	5.62	1.02
34	10.0	118.88	4.78	15.0	155.15	5.04	0.77
Mean	13.7	195.00	5.19	13.5	208.90	5.27	0.96
SD	1.9	80.09	0.41	2.5	80.27	0.41	0.23
CV	13.8	41.07	7.83	18.3	38.43	7.73	24.25
Median	14.0	180.88	5.20	15.0	182.71	5.21	0.99
Geo Mean	13.5	180.09	5.18	13.3	193.65	5.25	0.93

Test/Ref Ratio	
Ratio of Means %	93.35
Ratio of Geo Means %	93.00
Avg of Individual Ratios	0.96
90% C.I.	86%-99%
Intra-CV	16.07%

Fig. 10C

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on May 2, 2007, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

Richard L. Horwitz
POTTER ANDERSON & CORROON LLP

and that I caused copies to be served upon the following in the manner indicated:

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